CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215256Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 215256
Supplement #:	Original
Drug Name:	Semaglutide
Indication(s):	Adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management (b) (4) in adult patients with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (excess weight) in the presence of at least one weight-related comorbid condition
Applicant:	Novo Nordisk, Inc
Date(s):	Submitted: 12/04/2020
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	Review Due: 5/11/2021
	PDUFA: 6/04/2021
Review Priority:	Priority
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Statistical Reviewer:	Kyunghee K. Song, PhD
Concurring Reviewers:	Feng Li, PhD, Team Leader
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Medical Division:	Division of Diabetes, Lipid Disorders, and Obesity Products
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1 EXECUTIVE SUMMARY

Novo Nordisk submitted an original NDA for semaglutide as an adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management (b) (4) (b) (4) in adult patients with an initial Body Mass Index (BMI) of 30 kg/m^2 or greater (obesity), or 27 kg/m^2 or greater (excess weight) in the presence of at least one weight-related comorbid condition.

Four Phase 3 trials were reviewed as part of this NDA submission. In this review, the trials are referred to as STEP 1, STEP 2, STEP 3, and STEP 4. The proposed therapeutic and maintenance dose is semaglutide 2.4 mg subcutaneous injection once weekly. These trials were 68-week, randomized, double-blind, placebo-controlled, and the study subjects received either semaglutide 2.4 mg or placebo once weekly. In STEP 1, STEP 2, and STEP 3, there were 16 weeks of dose escalation and 52 weeks on maintenance dose. In STEP 4, subjects were randomized to either continue treatment or switch to placebo after a 20-week run-in period.

For STEP 1, STEP 2 and STEP 3, the primary endpoints were the percent change from baseline to Week 68 and the proportion of subjects who had at least 5% loss in body weight from baseline to Week 68. For STEP 4, the primary endpoint was the percent change in body weight from randomization (Week 20) to Week 68. The primary efficacy results demonstrated the efficacy for weight loss at Week 68, and the results are shown in Table 1. Missing values were handled using retrieved-subjects multiple imputation approach for the primary analysis.

Table 1: Percent Change in Body Weight from Baseline to Week 68

Primary endpoint: Percent change in body weight				
		N	LS mean[1] (SE)	Treatment Difference [95% CI]; p-value
STEP 1	Semaglutide 2.4 mg	1306	-14.85 (0.29)	-12.44 [-13.26, -11.61]; <0.0001
	Placebo	655	-2.42 (0.31)	
STEP 2	Semaglutide 2.4 mg	404	-9.64 (0.36)	-6.21 [-7.28, -5.15]; <0.0001
	Placebo	403	-3.42 (0.41)	
STEP 3	Semaglutide 2.4 mg	407	-15.97 (0.55)	-10.26 [-11.83, -8.69]; <0.0001
	Placebo	204	-5.71 (0.59)	
STEP 4*	Semaglutide 2.4 mg	535	-7.88 (0.36)	-14.75 [-15.99, -13.51]; <0.0001
	Placebo	268	6.87 (0.52)	
Primary endpoint: Proportion of subjects who had ≥5% body weight loss				
			Proportion[2] (%)	Treatment Difference [95% CI]; p-value
STEP 1	Semaglutide 2.4 mg	1306	83.47	52.41 [48.06, 56.75]; <0.0001
	Placebo	655	31.07	
STEP 2	Semaglutide 2.4 mg	404	67.44	37.25 [30.68, 43.81]; <0.0001
	Placebo	403	30.20	
STEP 3	Semaglutide 2.4 mg	407	84.79	37.04 [28.90, 45.19]; <0.0001
	Placebo	204	47.75	

Abbreviations: N=number of subjects randomized; LS mean=least squares mean; SE=standard error; CI=confidence interval; [1]Model based estimates using an analysis of covariance model included treatment (and stratification factors in STEP 2) as a fixed effect and baseline value as a covariate; [2]Estimates using a logistic regression with treatment (and stratification factors in STEP 2) as a factor and baseline body weight (kg) as a covariate. *In STEP 4, baseline was at Week 20 (randomization)

There were no major statistical issues found during the review of this submission. Efficacy in comparison to placebo was further supported by key secondary endpoints specified in each trial. Based on information from a clinical reviewer, it seems there were no major safety concerns identified that could impact the approval of the product.

Collectively, the studies provided evidence of a robust treatment effect for the study population. Based on findings from these efficacy studies, I recommend approval for the proposed indication.

2 INTRODUCTION

2.1 Overview

Semaglutide, a long-acting glucagon-like peptide -1 (GLP-1) analogue, has a 94% homology to human GLP-1 and is a selective GLP-1 receptor agonist (GLP-1 RA) with a long half-life suitable for once-weekly dosing. Semaglutide 0.5 mg and 1 mg, for once-weekly subcutaneous (s.c.) administration, is approved under the tradename Ozempic® as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes (T2D). GLP-1 RAs reduce body weight by lowering energy intake via induced feelings of satiety and fullness and by lowering feeling of hunger. This is consistent with the normal physiological effect of native GLP-1; GLP-1 is a known physiological regulator of appetite and GLP-1 receptors are present in several areas of the brain involved in appetite regulation.

The trials were designed to show that semaglutide subcutaneous injection (s.c.) 2.4 mg once-weekly, as an adjunct to a reduced-calorie diet and increased physical activity, is an effective and safe option for treatment of overweight or obesity. The STEP program consisted of 4 phase 3 trials:

- Trial ID: NN9536-4373 (STEP 1), Titled “Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity”
- Trial ID: NN9536-4374 (STEP 2), Titled “Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity and type 2 diabetes”
- Trial ID: NN9536-4375 (STEP 3), Titled “Effect and safety of semaglutide 2.4 mg once-weekly as adjunct to intensive behavioral therapy in subjects with overweight or obesity”
- Trial ID: NN9536-4376 (STEP 4), Titled “Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity who have reached target dose during run-in period”

The applicant complied with the statistical comments conveyed during the IND stage of this submission (IND 126360).

2.2 Data Sources

Materials for this statistical review, including the data and clinical study reports (CSR), were submitted electronically under the network path location:
\\CDSESUB1\evsprod\NDA215256\0001\m5\datasets\nn9536-4373 for STEP 1,
\\CDSESUB1\evsprod\NDA215256\0001\m5\datasets\nn9536-4374 for STEP 2,
\\CDSESUB1\evsprod\NDA215256\0001\m5\datasets\nn9536-4375 for STEP 3, and
\\CDSESUB1\evsprod\NDA215256\0001\m5\datasets\nn9536-4376 for STEP 4.

The information necessary for the statistical review was contained in Module 1 (cover letter, previous correspondence, labeling) and Module 5 (clinical study report, protocols, amendments, statistical analysis plan, datasets and programs).

In addition, the applicant's response to the statistics information request for a list of programs (codes) for subgroup analyses was submitted (1/15/2021) electronically and located under the network path \\CDSESUB1\evsprod\NDA215256\0004.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted efficacy data and analyses are generally acceptable in quality and documentation. The statistical reviewer was able to reproduce the results of primary and important secondary analyses and performed additional analysis as needed.

Blinding procedures were described in the study reports and acceptable.

3.2 Evaluation of Efficacy

Efficacy analysis procedures were pre-specified in the protocol and these analysis procedures were followed generally according to the protocol.

3.2.1 Study Design and Endpoints

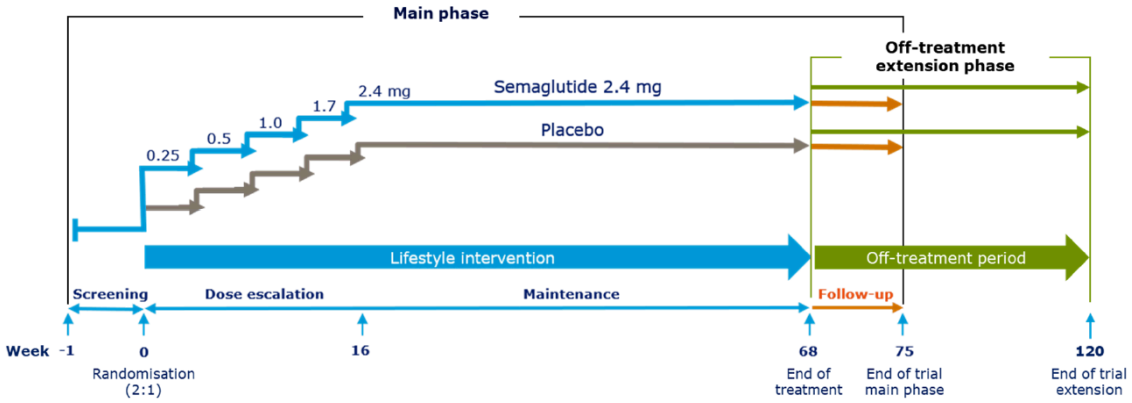
STEP 1
The trial was a multicenter, multinational trial comprising of a 68-week randomized, double-blind, 2-armed, placebo-controlled main phase and 52-week off-treatment extension phase. The trial included an initial 16-week dose-escalation period during which the dose was gradually increased to the maintenance dose of 2.4 mg once-weekly (ow). Treatment was continued on the maintenance dose of 2.4 mg ow for an additional 52 weeks until Week 68 (end of treatment). A follow-up visit for safety assessment was scheduled 7 weeks after end of treatment.

The study population consisted of,

- Male or females ≥18 years of age at the time of signing informed consent
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease
- History of at least one self-reported unsuccessful dietary effort to lose body weight

The trial design used for this study is shown in Figure 1.

Figure 1: Trial design (STEP 1)



[Source: page 35 of Clinical Study Report (CSR)]

In the main phase, 1961 subjects were randomized in a 2:1 ratio to receive either semaglutide s.c. 2.4 mg ow (1306 subjects) or placebo ow (655 subjects). The trial was conducted at 129 sites in 16 countries.

The primary objective was to compare the effect of semaglutide s.c. 2.4 mg ow vs. placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity on body weight (bw).

Primary endpoints

1. Percent (%) change from baseline to Week 68 in bw

   Percent change from baseline to Week 68 in bw was defined as

$$\%\ \text{weight change} = \frac{(\text{body weight at week 68} - \text{body weight at baseline})}{\text{body weight at baseline}} \times 100.$$

2. Proportion of subjects who achieved (yes/no) bw reduction ≥5% from baseline after Week 68 (5% responders)

Key secondary endpoints

3. Proportion of subjects who achieved (yes/no) bw reduction ≥10% from baseline after 68 weeks
4. Proportion of subjects who achieved (yes/no) bw reduction ≥15% from baseline after 68 weeks
5. Change from baseline to Week 68 in waist circumference (cm)
6. Change from baseline to Week 68 in systolic blood pressure (mmHg)
7. Change from baseline to Week 68 in physical functioning score (Short Form 36 v2.0 acute (SF-36))
8. Change from baseline to Week 68 in physical function domain (5-items) score (Impact of Weight on Quality of Life-Lite for Clinical Trials (IWQoL-Lite-CT))

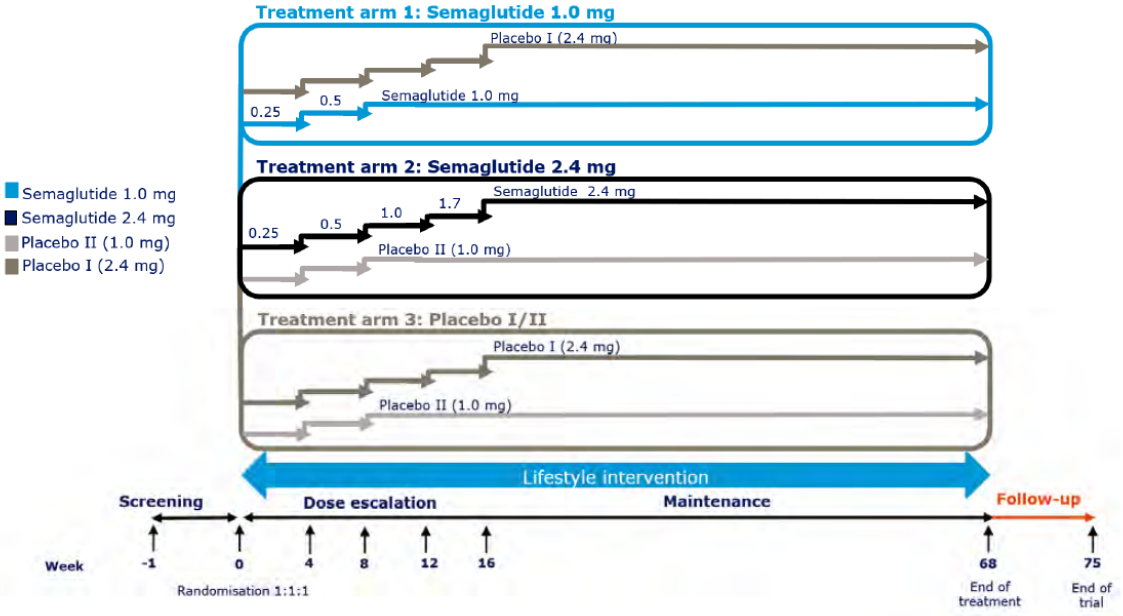
Note: A fixed sequence (as numbered above) statistical testing hierarchy was implemented for the primary and key secondary endpoints and it also applied to STEP 2, STEP 3, and STEP 4.

STEP 2

The trial was a multicenter, multinational trial comprising of a 68-week randomized, double-blind, double-dummy, 3-armed, placebo-controlled main phase and 7-week off-treatment extension phase. The trial included an initial dose escalation period of 8 weeks for the semaglutide 1.0 mg treatment group and of 16 weeks for the semaglutide 2.4 mg treatment group. Treatment was continued on the maintenance dose of 2.4 mg ow for an additional 52 weeks, or on semaglutide 1.0 mg for an additional 60 weeks, until Week 68.

The trial design used for this study is shown in Figure 2 .

Figure 2: Trial Design (STEP 2)



[Source: page 38 of Clinical Study Report (CSR)]

A total of 1210 subjects were randomized in a 1:1:1 ratio to receive either semaglutide 2.4 mg (404 subjects), semaglutide 1.0 mg (403 subjects), or placebo (403 subjects). The trial was conducted at 149 sites in 12 countries.

The randomization was stratified by these two factors: diabetes treatment status (diet/exercise or metformin or Sodium-GLucose co-Transporter 2 inhibitors (SGLT2i) vs SulphonylUrea (SU) or glitazone or >1 Oral Antidiabetic Drugs (OADs)) and HbA_{1c} category (<8.5% vs ≥8.5%).

The study population consisted of,

- Male or females ≥18 years of age at the time of signing informed consent
- BMI ≥27 kg/m^2
- History of at least one self-reported unsuccessful dietary effort to lose body weight

- Diagnosed with Type 2 Diabetes (T2D) ≥180 days prior to the day of screening
- Subjects treated with either:
    - Diet and exercise alone or stable treatment with metformin, SU, SGLT2i, glitazone as single agent therapy or
    - Up to 3 OADs (metformin, SU, SGLT2i or glitazone) according to local label

  Any approved and marketed metformin, glitazone, SGLT2i or SU product or combination product were allowed. Treatment with oral agents should be stable for at least 90 days prior to screening
- HbA_{1c} 7-10% (53-86 mmol/mol) (both inclusive)

The primary objective was to compare the effect of semaglutide s.c. 2.4 mg ow vs. placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity and Type 2 diabetes (T2D) on body weight.

Primary endpoints

1. Percent (%) change from baseline to Week 68 in bw
2. Proportion of subjects who achieved (yes/no) bw reduction ≥5% from baseline after Week 68 (5% responders)

Key secondary endpoints

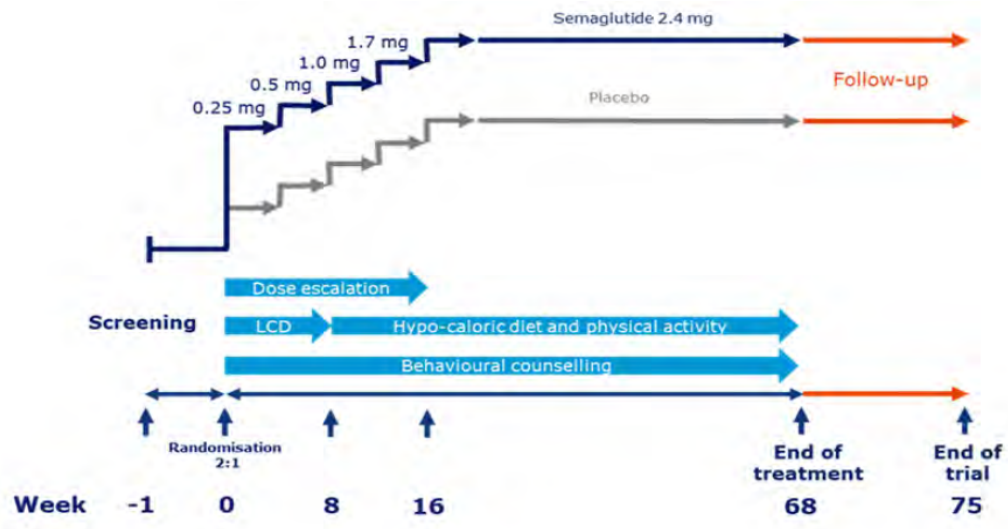
3. Proportion of subjects who achieved (yes/no) bw reduction ≥10% from baseline after 68 weeks
4. Proportion of subjects who achieved (yes/no) bw reduction ≥15% from baseline after 68 weeks
5. Change from baseline to Week 68 in waist circumference (cm)
6. %change in bw from baseline to Week 68: semaglutide 2.4 mg vs semaglutide 1.0 mg
7. % change from baseline to Week 68 in HbA_{1c} (mmol/mol)
8. Change from baseline to Week 68 in systolic blood pressure (mmHg)
9. Change from baseline to Week 68 in physical functioning score (SF-36)
10. Change from baseline to Week 68 in physical function domain (5-items) score (IWQoL-Lite-CT)

STEP 3

The trial was a multicenter trial (in US) comprising of a 68-week randomized, double-blind, 2-armed, placebo-controlled treatment period and a 7-week follow-up period. The trial included an initial 16-week dose-escalation period during which the dose was gradually increased to the maintenance dose of 2.4 mg ow. Treatment was continued on the maintenance dose of 2.4 mg ow for an additional 52 weeks until Week 68. A follow-up visit was scheduled 7 weeks after end of treatment.

The trial design used for this study is shown in Figure 3.

Figure 3: Trial design (STEP 3)



[Source: page 35 of Clinical Study Report (CSR)]

The study population consisted of,

- Male or females ≥18 years of age at the time of signing informed consent
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease
- History of at least one self-reported unsuccessful dietary effort to lose body weight

A total of 611 subjects were randomized in a 2:1 ratio to receive either semaglutide 2.4 mg (407 subjects) or placebo (204 subjects). The trial was conducted at 41 sites in the US.

The primary objective was to compare the effect of semaglutide s.c. 2.4 mg ow vs placebo as an adjunct to Intensive Behavioural Therapy (IBT) in subjects with overweight or obesity, on body weight.

<u>Primary endpoints</u>

1. Percent (%) change from baseline to Week 68 in bw
2. Proportion of subjects who achieved (yes/no) bw reduction ≥5% from baseline after Week 68 (5% responders)

<u>Key secondary endpoints</u>

3. Proportion of subjects who achieved (yes/no) bw reduction ≥10% from baseline after 68 weeks
4. Proportion of subjects who achieved (yes/no) bw reduction ≥15% from baseline after 68 weeks
5. Change from baseline to Week 68 in waist circumference (cm)
6. Change from baseline to Week 68 in systolic blood pressure (mmHg)
7. Change from baseline to Week 68 in physical functioning score (SF-36)

STEP 4

The trial was a multicenter, multinational, 2-armed, randomized, double-blind, placebo-controlled, withdrawal trial comprising of a 20-week run-in period (including 16 weeks of dose escalation), a 48-week period on maintenance dose and a 7-week off-treatment follow-up period. Subjects were randomized after the run-in period at Week 20.

The study population consisted of,

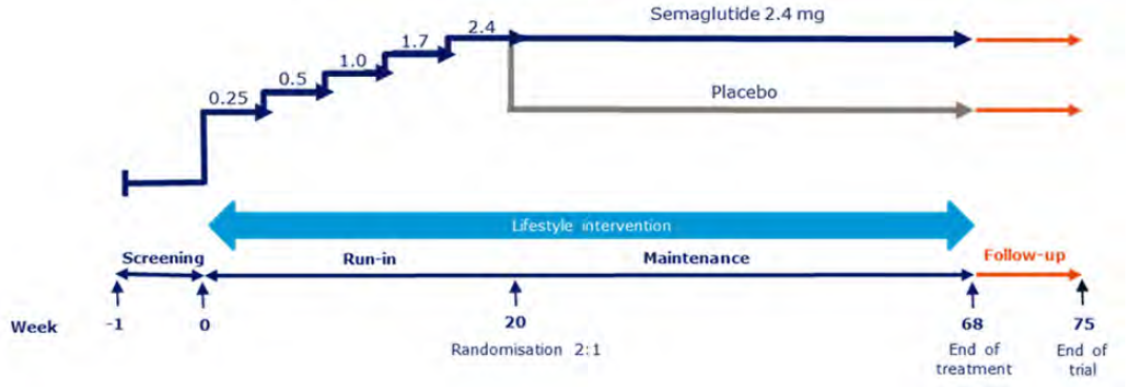
- Male or females ≥18 years of age at the time of signing informed consent
- BMI ≥30 kg/m^2 or ≥27 kg/m^2 with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease
- History of at least one self-reported unsuccessful dietary effort to lose body weight

Subjects who had entered the run-in period were eligible for randomization if the following randomization criteria were satisfied:

- attended the randomization visit (Week 20) and
- had escalated to target dose after 16 weeks since week 0 and
- were at target dose at the randomization visit (Week 20)

The trial design used for this study is shown in Figure 4.

Figure 4: Trial design (STEP 4)



[Source: page 38 of Clinical Study Report (CSR)]

A total of 902 subjects were included in the run-in period and exposed to semaglutide 2.4 mg s.c. ow. Of the 902 subjects, 99 subjects discontinued the treatment before randomization. Of the 99 subjects who discontinued, 48 were due to adverse event, 19 were due to being run-in failure, 11 were due to withdrawal of consent, 9 were due to "other," 8 were due to lost-to-follow-up, 2 were due to safety concern, 1 was due to pregnancy and 1 was due to protocol violation. A total of 803 subjects were randomized in a 2:1 ratio to receive either semaglutide 2.4 mg (535 subjects) or placebo (268 subjects).

The trial was conducted at 73 sites in 10 countries.

The primary objective was to compare the effect of semaglutide s.c. 2.4 mg ow vs. placebo as an adjunct to reduced-calorie diet and increased physical activity in subjects with overweight or obesity who had reached target dose of semaglutide during the run-in period.

Primary endpoint

1. Percent (%) change from randomization (Week 20) to Week 68 in bw

Key secondary endpoints

2. Change from randomization to Week 68 in waist circumference (cm)
3. Change from randomization to Week 68 in systolic blood pressure (mmHg)
4. Change from randomization to Week 68 in physical functioning score (SF-36)

3.2.2 Statistical Methodologies

The statistical methods were nearly identical across the trials. The primary estimand quantified the treatment effect in all randomized subjects regardless of adherence to treatment and regardless of initiation of other anti-obesity therapies (treatment policy estimand), and this estimand covered all efficacy related objectives.

The in-trial period was defined as the uninterrupted time interval from Week 0 (see Trial Design in Section 2.2.1 of this review) to date of last contact with trial site.

The on-treatment period was defined as all times which were considered as on-treatment. In general, the on-treatment period was from the date of first trial product administration to date of last trial product administration (+14 days) excluding potential off-treatment time intervals triggered by at least two consecutive missed doses. For the evaluation of adverse events, the lag time for each on-treatment time interval was 7 weeks.

The last available and eligible observation at or before randomization was used as the baseline value when baseline data were missing. If no assessments were available, the mean of baseline values across all subjects was used as the baseline value.

Analysis population

The full analysis set (FAS) included all randomized subjects according to the intention-to-treat principle.

The safety analysis set (SAS) included all randomized subjects exposed to at least one dose of randomized treatment.

Primary endpoint

Primary analysis

The analysis model for %weight change was an analysis of covariance model (ANCOVA) with randomized treatment as a factor and baseline body weight (kg) as a covariate. The estimated

treatment difference between semaglutide 2.4 mg and placebo was reported with the associated 2-sided 95% confidence interval (CI) and corresponding p-value. For STEP 2, stratification groups (oral anti-diabetic drug (OAD) treatment and HbA_{1c} category) were added as factors.

The analysis model for the 5% responder endpoint was a logistic regression using randomized treatment as a factor and baseline body weight (kg) as a covariate. The estimated proportion of the 5% responder was reported with the associated 2-sided 95% CI and corresponding p-value. For STEP 2, stratification groups (oral anti-diabetic drug (OAD) treatment and HbA_{1c} category) were added as factors.

For STEP 4, the baseline values were values at Week 20 (at randomization).

Handling of missing Week 68 values

All available data at Week 68 were used and missing values at Week 68 were imputed, and the endpoints were derived from the imputed values. To describe imputation approach, subjects were categorized as below:

- AT: subjects who completed the trial on randomized treatment with an assessment at Week 68 (included those that stopped and restarted trial product)
- AD: subjects who discontinued randomized treatment prematurely but returned to have an assessment at Week 68 (retrieved subjects)
- MT: subjects who completed the trial on randomized treatment without an assessment at Week 68 (included those that stopped and restarted trial product)
- MD: subjects who discontinued randomized treatment prematurely and did not return to have an assessment at Week 68 (non-retrieved subjects)

The primary imputation approach for the primary estimand was a multiple imputation. Missing body weight measurements at Week 68 for non-retrieved subjects (MD) were imputed using assessment from retrieved subjects (AD) in each randomized treatment arm. This was done according to the timing of last available observation on-treatment of body weight prior to Week 68. Missing body weight measurements at Week 68 for subjects on randomized treatment (MT) were imputed by sampling from available measurements at Week 68 from subjects on randomized treatment (AT) in the relevant randomized treatment arm.

A total of 1000 complete datasets were generated for the analysis and the final results were integrated using Rubin's rule.

<u>Sensitivity analysis</u>

- Jump to reference multiple imputation (J2R-MI): Missing values at Week 68 for both treatment groups (MT and MD) were imputed by sampling among all available assessment at Week 68 in the placebo group (AT and AD). This approach assumed that subjects instantly after discontinuation lost any effect of randomized treatment beyond what could be expected from placebo as adjunct to reduced-diet and increased physical activity

- Single imputation: Two single imputation methods were used; S1-S1 and S2-S1. For S1-S1, missing values at Week 68 for non-retrieved subjects were imputed by using a weight regain rate of 0.3 kg/month after last available observation (LAO) but truncated at no change from baseline whenever the extrapolation would lead to a positive weight gain relative to baseline. If a subject's weight at drug discontinuation represented a gain in weight relative to baseline, no additional gain was imputed, and the unfavorable gain was carried forward to Week 68. The weight regain imputation was done for both randomized treatment groups. For S2-S1, only semaglutide used the regain rate while placebo used LAO. For both methods, missing values at Week 68 for subjects on randomized treatment were imputed by LAO.
- Tipping point multiple imputation: Missing data were imputed according to the primary multiple imputation approach. Then a penalty was added to the imputed values at Week 68. The 2-dimensional space of penalties covering the range from -30% to 30% was explored for both treatment groups.
- MMRM: All assessments regardless of adherence to randomized treatment were used. For the 5% responder analysis, individual missing values for body weight at Week 68 was predicted using a Mixed Model Repeated Measures (MMRM) method and used to classify each subject as 5% responder or not. This classification was then be analyzed using the same logistic regression model as in the primary analysis of the primary estimand.
- Non-responder analysis: Subjects with missing 68-week assessment were considered non-responders.

Key secondary endpoints

Primary analysis
All key secondary endpoints were analyzed using the same imputation approach as used for the primary endpoints. The statistical model for continuous endpoints was an ANCOVA with the same factors used for the primary endpoint and the baseline assessment of the respective endpoint as a covariate. The statistical model for a responder endpoint was a logistic regression with the same factors used for the primary endpoint and the baseline assessment of the respective endpoint as a covariate.

For STEP 2, stratification groups (oral anti-diabetic drug (OAD) treatment and HbA_{1c}) were added as factors.

Sensitivity analysis
For all continuous endpoints, a sensitivity analysis using J2R-MI imputation approach was carried out. For all binary endpoints, a sensitivity analysis using non-responder approach was performed.

Subgroup analyses for the primary efficacy endpoint
To assess the treatment effect across various subgroups, a subgroup and a treatment-by-subgroup interaction terms were added in the primary analysis model.

Multiplicity considerations

The overall type I error was controlled by a hierarchical testing approach. Statistical significance of the primary endpoint(s) was required before testing for the first key secondary endpoint. Inferential conclusions about successive key secondary endpoints required statistical significance of the prior endpoint within the hierarchy and this hierarchy testing procedure was prespecified.

Note: To account for unequal randomization for the primary analysis in STEP 1, STEP 3 and STEP 4, I ran ANCOVA models using unequal variance for treatment groups and compared the results to the applicant's results. There were either almost no numerical differences or very minor numerical differences between the two results.

Analysis of safety endpoints

Adverse events were defined as "treatment-emergent" (TEAE), if the onset of the event occurred in the on-treatment period. TEAEs and Serious adverse events (SAEs) were summarized by descriptive statistics. No formal statistical inferences were carried out.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition

For each STEP study, the summary of the subject disposition is given in

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Table 2 to

Table 5. Across the trials, the proportion of subjects who completed treatment was ranged from 82.9% to 94.2% for the semaglutide group and from 77.6% to 88.4% in the placebo group. Main reason for discontinuing treatment was adverse event in most studies followed by “other” and lost to follow-up. The proportion of subjects who withdrew from the trial was ranged from 1.5% to 7.6% in the semaglutide group and from 3.0% to 7.0% in the placebo group.

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Table 2: Patient Disposition in STEP 1

	Sema 2.4 mg	**Placebo**	**Total**
Randomized	1306	655	1961
completed treatment	**1083 (82.9%)**	**508 (77.6%)**	**1591 (81.1%)**
discontinued treatment	223 (17.1%)	147 (22.4%)	370 (18.9%)
adverse event	91 (7.0%)	21 (3.2%)	112 (5.7%)
protocol violation	3 (0.2%)	5 (0.8%)	8 (0.4%)
pregnancy	7 (0.5%)	3 (0.5%)	10 (0.5%)
lack of efficacy	1 (<0.1%)	16 (2.4%)	17 (0.9%)
at the discretion of the investigator	4 (0.3%)	1 (0.2%)	5 (0.3%)
safety concerns as judged by the investigator	15 (1.1%)	0	15 (0.8%)
withdrawal of consent	9 (0.7%)	10 (1.5%)	19 (1.0%)
lost to follow-up	26 (2.0%)	25 (3.8%)	51 (2.6%)
other	67 (5.1%)	66 (10.1%)	133 (6.8%)
completed trial	**1240 (94.9%)**	**609 (93.0%)**	**1849 (94.3%)**
withdrawal from the trial	66 (5.1%)	46 (7.0%)	112 (5.7%)
withdrawal by subject	26 (2.0%)	17 (2.6%)	43 (2.2%)
lost to follow-up	39 (3.0%)	28 (4.3%)	67 (3.4%)
death	1 (<0.1%)	1 (0.2%)	2 (0.1%)

[Source: excerpted from page 65 of CSR]

Table 3: Patient Disposition in STEP 2

	Sema 1.0 mg	**Sema 2.4 mg**	**Placebo**	**Total**
Randomized	403	404	403	1210
completed treatment	**354 (87.8%)**	**357 (88.4%)**	**347 (86.1%)**	**1058 (87.4%)**
discontinued treatment	49 (12.2%)	47 (11.6%)	56 (13.9%)	152 (12.6%)
adverse event	19 (4.7%)	26 (6.4%)	13 (3.2%)	58 (4.8%)
protocol violation	5 (1.2%)	1 (0.2%)	7 (1.7%)	13 (1.1%)
pregnancy	0	0	0	0
lack of efficacy	0	0	0	0
at the discretion of the investigator	2 (0.5%)	0	1 (0.2%)	3 (0.2%)
safety concerns as judged by the investigator	1 (0.2%)	1 (0.2%)	0	2 (0.2%)
withdrawal of consent	5 (1.2%)	2 (0.5%)	7 (1.7%)	14 (1.2%)
lost to follow-up	2 (0.5%)	5 (1.2%)	3 (0.7%)	10 (0.8%)
other	15 (3.7%)	12 (3.0%)	25 (6.2%)	52 (4.3%)
completed trial	**390 (96.8%)**	**391 (96.8%)**	**383 (95.0%)**	**1164 (96.2%)**
withdrawal from the trial	13 (3.2%)	13 (3.2%)	20 (5.0%)	46 (3.8%)
withdrawal by subject	10 (2.5%)	5 (1.2%)	12 (3.0%)	27 (2.2%)
lost to follow-up	2 (0.5%)	7 (1.7%)	7 (1.7%)	16 (1.3%)
death	1 (0.2%)	1 (0.2%)	1 (0.2%)	3 (0.2%)

[Source: excerpted from page 73 of CSR]

Table 4: Patient Disposition in STEP 3

	Sema 2.4 mg	**Placebo**	**Total**
Randomized	407	204	611
completed treatment	**339 (83.3%)**	**166 (81.4%)**	**505 (82.7%)**
discontinued treatment	68 (16.7%)	38 (18.6%)	106 (17.3%)
adverse event	26 (6.4%)	6 (2.9%)	32 (5.2%)
protocol violation	0	1 (0.5%)	1 (0.2%)
pregnancy	1 (0.2%)	2 (1.0%)	3 (0.5%)
lack of efficacy	0	1 (0.5%)	1 (0.2%)
at the discretion of the investigator	1 (0.2%)	0	1 (0.2%)
safety concerns as judged by the investigator	1 (0.2%)	2 (1.0%)	3 (0.5%)
withdrawal of consent	4 (1.0%)	3 (1.5%)	7 (1.1%)
lost to follow-up	18 (4.4%)	7 (3.4%)	25 (4.1%)
other	17 (4.2%)	16 (7.8%)	33 (5.4%)
completed trial	**376 (92.4%)**	**191 (93.6%)**	**567 (92.8%)**
withdrawal from the trial	31 (7.6%)	13 (6.4%)	44 (7.2%)
withdrawal by subject	7 (1.7%)	3 (1.5%)	10 (1.6%)
lost to follow-up	24 (5.9%)	10 (4.9%)	34 (5.6%)
death	0	0	0

[Source: excerpted from page 64 of CSR]

Table 5: Patient Disposition in STEP 4

	Sema 2.4 mg	Placebo	Total
Randomized (at Week 20)	535	268	803
completed treatment	**504 (94.2%)**	**237 (88.4%)**	**741 (92.3%)**
discontinued treatment	31 (5.8%)	31 (11.6%)	62 (7.7%)
adverse event	13 (2.4%)	6 (2.2%)	19 (2.4%)
protocol violation	1 (0.2%)	0	1 (0.1%)
pregnancy	2 (0.4%)	0	2 (0.2%)
lack of efficacy	0	0	0
at the discretion of the investigator	0	0	0
safety concerns as judged by the investigator	0	0	0
withdrawal of consent	1 (0.2%)	1 (0.4%)	2 (0.2%)
lost to follow-up	2 (0.4%)	1 (0.4%)	3 (0.4%)
other	12 (2.2%)	23 (8.6%)	35 (4.4%)
completed trial	**527 (98.5%)**	**260 (97.0%)**	**787 (98.0%)**
withdrawal from the trial	8 (1.5%)	8 (3.0%)	16 (2.0%)
withdrawal by subject	2 (0.4%)	4 (1.5%)	6 (0.7%)
lost to follow-up	5 (0.9%)	3 (1.1%)	8 (1.0%)
death	1 (0.2%)	1 (0.4%)	2 (0.2%)

[Source: excerpted from page 66 of CSR]

Demographic and other baseline characteristics

Baseline demographics are shown in

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Table 6 to

Table 9. The demographics and baseline characteristics were generally similar across treatment groups. The majority of the study population was female subjects (74.1% to 81.0%) in all trials except STEP 2. In STEP 2, approximately half of the subjects were males (49.1%). The study population was largely white (62.1% to 83.7%) in all trials. The mean ages were similar between trials (mean=46 years of age) except STEP 2 (mean=55 years of age).

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Table 6: Baseline Demographics of Subjects in STEP 1

		Semaglutide 2.4 mg	Placebo	Total
	N	1306	655	1961
Age (years)	18- <65	1198 (91.7%)	607 (92.7%)	1805 (92.0%)
	65 -<75	99 (7.6%)	46 (7.0%)	145 (7.4%)
	75- <85	8 (0.6%)	2 (0.3%)	10 (0.5%)
	85 or >85	1 (<0.1%)	0	1 (0.1%)
Sex	Female	955 (73.1%)	498 (76.0%)	1453 (74.1%)
	Male	351 (26.9%)	157 (24.0%)	508 (25.9%)
Ethnic Origin	Not Hispanic or Latino	1118 (85.6%)	551 (84.1%)	1669 (85.1%)
	Hispanic or Latino	150 (11.5%)	86 (13.1%)	236 (12.0%)
	Not Applicable	38 (2.9%)	17 (2.6%)	55 (2.8%)
	Unknown	0	1 (0.2%)	1 (0.1%)
Race	White	973 (74.5%)	499 (76.2%)	1472 (75.1%)
	Asian	181 (13.9%)	80 (12.2%)	261 (13.3%)
	Black or African American	72 (5.5%)	39 (6.0%)	111 (5.7%)
	American Indian or Alaska Native	17 (1.3%)	10 (1.5%)	27 (1.4%)
	Native Hawaiian or Other Pacific Islander	0	2 (0.3%)	2 (0.1%)
	Other	25 (1.9%)	8 (1.2%)	33 (1.7%)
	Not Applicable	38 (2.9%)	17 (2.6%)	55 (2.8%)
Region	Asia (excluding East Asia)	82 (6.3%)	35 (5.3%)	117 (6.0%)
	East Asia	93 (7.1%)	42 (6.4%)	135 (6.9%)
	Europe	501 (38.4%)	247 (37.7%)	748 (38.1%)
	North America	544 (41.7%)	282 (43.1%)	826 (42.1%)
	South America	86 (6.6%)	49 (7.5%)	135 (6.9%)
BMI (kg/m^2)	<30	81 (6.2%)	36 (5.5%)	117 (6.0%)
	30 -<35	436 (33.4%)	207 (31.6%)	643 (32.8%)
	35 -<40	406 (31.1%)	208 (31.8%)	614 (31.3%)
	40 or greater	383 (29.3%)	204 (31.1%)	587 (29.9%)
Age (years): Mean (SD)		46 (13)	47 (12)	46 (13)
Body Weight (kg): Mean (SD)		105.4 (22.1)	105.2 (21.5)	105.3 (21.9)
BMI (kg/m^2): Mean (SD)		37.8 (6.7)	38.0 (6.5)	37.9 (6.7)
Waist Circumference (cm): Mean (SD)		114.6 (14.8)	114.8 (14.4)	114.7 (14.6)
HBA_{1c} (%): Mean (SD)		5.7 (0.3)	5.7 (0.3)	5.7 (0.3)

Abbreviations: N=number of patients randomized; BMI=Body Mass Index; SD=Standard Deviation; cell contents for Age (years), Sex, Ethnic Origin, Race, Region, BMI (kg/m^2) are frequencies with relative frequencies in parentheses; For all other characteristics are mean and the standard deviation in parentheses; [Source: excerpted from page 69 of CSR]

Table 7: Baseline Demographics of Subjects in STEP 2

		Semaglutide 1.0 mg	Semaglutide 2.4 mg	Placebo	Total
	N	403	404	403	1210
Age (years)	18- <65	320 (79.4%)	316 (78.2%)	317 (78.7%)	953 (78.8%)
	65 -<75	78 (19.4%)	78 (19.3%)	78 (19.4%)	234 (19.3%)
	75- <85	5 (1.2%)	10 (2.5%)	8 (2.0%)	23 (1.9%)
	85 or >85	0	0	0	0
Sex	Female	203 (50.4%)	223 (55.2%)	190 (47.1%)	616 (50.9%)
	Male	200 (49.6%)	181 (44.8%)	213 (52.9%)	594 (49.1%)
Ethnic Origin	Not Hispanic or Latino	344 (85.4%)	357 (88.4%)	354 (87.8%)	1055 (87.2%)
	Hispanic or Latino	59 (14.6%)	47 (11.6%)	49 (12.2%)	155 (12.8%)
	Not Applicable	0	0	0	0
	Unknown	0	0	0	0
Race	White	272 (67.5%)	237 (58.7%)	242 (60.0%)	751 (62.1%)
	Asian	97 (24.1%)	112 (27.7%)	108 (26.8%)	317 (26.2%)
	Black or African American	28 (6.9%)	35 (8.7%)	37 (9.2%)	100 (8.3%)
	American Indian or Alaska Native	0	4 (1.0%)	2 (0.5%)	6 (0.5%)
	Native Hawaiian or Other Pacific Islander	0	0	1 (0.2%)	1 (0.08%)
	Other	6 (1.5%)	16 (4.0%)	13 (3.2%)	35 (2.9%)
	Not Applicable	0	0	0	0
Region	Africa	20 (5.0%)	12 (3.0%)	18 (4.5%)	50 (4.1%)
	Asia (excluding East Asia)	57 (14.1%)	79 (19.6%)	66 (16.4%)	202 (16.7%)
	East Asia	36 (8.9%)	42 (10.4%)	47 (11.7%)	125 (10.3%)
	Europe	121 (30.0%)	108 (26.7%)	126 (31.3%)	355 (29.3%)
	North America	141 (35.0%)	146 (36.1%)	129 (32.0%)	416 (34.4%)
	South America	28 (6.9%)	17 (4.2%)	17 (4.2%)	62 (5.1%)
BMI (kg/m^2)	<30	66 (16.4%)	68 (16.8%)	77 (19.1%)	211 (17.4%)
	30 -<35	163 (40.4%)	140 (34.7%)	135 (33.5%)	438 (36.2%)
	35 -<40	100 (24.8%)	103 (25.5%)	97 (24.1%)	300 (24.8%)
	40 or greater	74 (18.4%)	93 (23.0%)	94 (23.3%)	261 (21.6%)
Age (years): Mean (SD)		56 (10)	55 (11)	55 (11)	55 (11)
Body Weight (kg): Mean (SD)		99.0 (21.1)	99.9 (22.5)	100.5 (20.9)	99.8 (21.5)
BMI (kg/m^2): Mean (SD)		35.3 (5.9)	35.9 (6.4)	35.9 (6.5)	35.7 (6.3)
Waist Circumference: Mean (SD)		113. 9 (14.0)	114.5 (14.3)	115.5 (13.9)	114.6 (14.1)
HbA_{1c}(%): Mean (SD)		8.1 (0.8)	81 (0.8)	8.1 (0.8)	8.1 (0.8)
Diabetes Duration (years): Mean (SD)		7.7 (5.9)	8.2 (6.2)	8.2* (6.2)	8.0 (6.1)

Abbreviations: N=number of patients randomized; BMI=Body Mass Index; SD=standard deviation; *Duration of diabetes was not available in one placebo subject; cell contents for Age (years), Sex, Ethnic Origin, Race, Region, BMI (kg/m^2) are frequencies with relative frequencies in parentheses; For all other characteristics are mean and the standard deviation in parentheses; [Source: excerpted from page 77 of CSR]

Table 8: Baseline Demographics of Subjects in STEP 3

		Semaglutide 2.4 mg	Placebo	Total
	N	407	204	611
Age (years)	18- <65	379 (93.1%)	186 (91.2%)	565 (92.5%)
	65 -<75	27 (6.6%)	16 (7.8%)	43 (7.0%)
	75- <85	1 (0.2%)	2 (1.0%)	3 (0.5%)
	85 or >85	0	0	0
Sex	Female	315 (77.4%)	180 (88.2%)	495 (81.0%)
	Male	92 (22.6%)	24 (11.8%)	116 (19.0%)
Ethnic Origin	Not Hispanic or Latino	332 (81.6%)	158 (77.5%)	490 (80.2%)
	Hispanic or Latino	75 (18.4%)	46 (22.5%)	121 (19.8%)
	Not Applicable	0	0	0
	Unknown	0	0	0
Race	White	307 (75.4%)	158 (77.5%)	465 (76.1%)
	Asian	5 (1.2%)	6 (2.9%)	11 (1.8%)
	Black or African American	80 (19.7%)	36 (17.6%)	116 (19.0%)
	American Indian or Alaska Native	1 (0.2%)	0	1 (0.2%)
	Native Hawaiian or Other Pacific Islander	3 (0.7%)	0	3 (0.5%)
	Other	11 (2.7%)	4 (2.0%)	15 (2.5%)
	Not Applicable	0	0	0
BMI (kg/m^2)	<30	23 (5.7%)	15 (7.4%)	38 (6.2%)
	30 -<35	126 (31.0%)	58 (28.4%)	184 (30.1%)
	35 -<40	136 (33.4%)	76 (37.3%)	212 (34.7%)
	40 or greater	122 (30.0%)	55 (27.0%)	177 (29.0%)
Age (years): Mean (SD)		46 (13)	46 (13)	46 (13)
Body Weight (kg): Mean (SD)		106.9 (22.8)	103.7 (22.9)	105.8 (22.9)
BMI (kg/m^2): Mean (SD)		38.1 (6.7)	37.8 (6.9)	38.0 (6.7)
Waist Circumference (cm): Mean (SD)		113.6 (15.1)	111.8 (16.2)	113.0 (15.5)
HbA_{1c} (%): Mean (SD)		5.7 (0.3)	5.8 (0.3)	5.7 (0.3)

Abbreviations: N=number of patients randomized; BMI=Body Mass Index; SD=standard deviation; cell contents for Age (years), Sex, Ethnic Origin, Race, BMI (kg/m^2) are frequencies with relative frequencies in parentheses; For all other characteristics are mean and the standard deviation in parentheses; [Source: excerpted from page 67 of CSR]

Table 9: Baseline Demographics of Subjects in STEP 4 (at randomization (Week 20))

		Semaglutide 2.4 mg	Placebo	Total
	N	535	268	803
Age (years)	18- <65	503 (94.0%)	52 (94.0%)	755 (94.0%)
	65 -<75	29 (5.4%)	15 (5.6%)	44 (5.5%)
	75- <85	3 (0.6%)	1 (0.4%)	4 (0.5%)
	85 or >85	0	0	0
Sex	Female	429 (80.2%)	205 (76.5%)	634 (79.0%)
	Male	106 (19.8%)	63 (23.5%)	169 (21.0%)
Ethnic Origin	Not Hispanic or Latino	493 (92.1%)	247 (92.2%)	740 (92.2%)
	Hispanic or Latino	42 (7.9%)	21 (7.8%)	63 (7.8%)
	Not Applicable	0	0	0
	Unknown	0	0	0
Race	White	446 (83.4)	226 (84.3%)	672 (83.7%)
	Asian	15 (2.8%)	4 (1.5%)	19 (2.4%)
	Black or African American	69 (12.9%)	35 (13.1%)	104 (13.0%)
	American Indian or Alaska native	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0
	Other	5 (0.9%)	3 (1.1%)	8 (1.0%)
	Not Applicable	0	0	0
Region	Africa	45 (8.4%)	20 (7.5%)	65 (8.1%)
	Europe	282 (52.7%)	144 (53.7%)	426 (53.1%)
	North America	208 (38.9%)	104 (38.8%)	312 (38.9%)
BMI (kg/m^2)	<25	7 (1.3%)	9 (3.4%)	16 (2.0%)
	25- <30	153 (28.6%)	69 (25.7%)	222 (27.6%)
	30- <35	166 (31.0%)	97 (36.2%)	263 (32.8%)
	35- <40	116 (21.7%)	52 (19.4%)	168 (20.9%)
	40 or greater	93 (17.4%)	41 (15.3%)	134 (16.7%)
Age (years): Mean (SD)		47 (12)	46 (12)	46 (12)
Body Weight (kg): Mean (SD)		96.5 (22.5)	95.4 (22.2)	96.1 (22.6)
BMI (kg/m^2): Mean (SD)		34.5 (6.9)	34.1 (7.1)	34.4 (7.0)
Waist Circumference (cm): Mean (SD)		105.5 (15.9)	104.7 (16.9)	105.3 (16.2)
HbA_{1c} (%): Mean (SD)		5.4 (0.3)	5.4 (0.3)	5.4 (0.3)

Abbreviations: N=number of patients randomized; BMI=Body Mass Index; SD=standard deviation; cell contents for Age (years), Sex, Ethnic Origin, Race, Region, BMI (kg/m^2) are frequencies with relative frequencies in parentheses; For all other characteristics are mean and the standard deviation in parentheses; [Source: excerpted from page 70 of CSR]

3.2.4 Results and Conclusions

Missing Data

The amount of missing data at Week 68 are shown in Table 10 for each trial. Across the trials, the proportion of missing data ranged from 2.8% to 8.4% for semaglutide 2.4 mg and from 6.7%

to 11.9% for placebo. Most missing values were from subjects who did not complete treatment. As noted in Table 10, the number of observed values is the sum of the number of observed values from subjects who completed treatment (A) and the number of retrieved values from subjects who discontinued treatment (B). For the primary efficacy analysis, missing body weight measurements at Week 68 were imputed using assessment from retrieved subjects in each randomized treatment arm. Missing body weight measurements at Week 68 for subjects on treatment were imputed from available measurements at Week 68 from subjects on treatment in the relevant randomized treatment arm (Section 3.2.2 of this review).

Table 10: Summary of Missing Data

		N	Observed (A+B)	On treatment at Week 68 (A)	Retrieved subjects (B)	Missing
STEP 1	Sema 2.4 mg	1306	1212 (92.8%)	1077 (82.5%)	135 (10.3%)	94 (7.2%): complete trt: 6 discontinue trt: 88
	Placebo	655	577 (88.1%)	505 (77.1%)	72 (11.0%)	78 (11.9%): complete trt: 3 discontinue trt: 75
STEP 2	Sema 1.0 mg	403	380 (94.3%)	353 (87.6%)	27 (6.7%)	23 (5.7%): complete trt: 1 discontinue trt: 23
	Sema 2.4 mg	404	388 (96.0%)	356 (88.1%)	32 (7.9%)	16 (4.0%): complete trt: 1 discontinue trt: 15
	Placebo	403	376 (93.3%)	346 (85.9%)	30 (7.4%)	27 (6.7%): complete trt: 1 discontinue trt: 26
STEP 3	Sema 2.4 mg	407	373 (91.6%)	338 (83.0%)	35 (8.6%)	34 (8.4%): complete trt: 1 discontinue trt: 33
	Placebo	204	189 (92.6%)	165 (80.9%)	24 (11.8%)	15 (7.4%): complete trt: 1 discontinue trt: 14
STEP 4	Sema 2.4 mg	535	520 (97.2%)	502 (93.8%)	18 (3.4%)	15 (2.8%): complete trt: 2 discontinue trt: 13
	Placebo	268	250 (93.3%)	235 (87.7%)	15 (5.6%)	18 (6.7%): complete trt: 2 discontinue trt: 16

Abbreviations: N=number of subjects randomized; sema=semaglutide; cell content shows frequency and percentage relative to N in the parentheses; trt=treatment; [Source: Statistical Reviewer]

Primary endpoint results

Treatment with semaglutide (2.4 mg) resulted in a statistically significant more percent reduction in body weight in all 4 trials (

Table 11) compared to placebo. In STEP 4, the subjects were randomized to either continue semaglutide or switch to placebo after the 20-week run-in period. Subjects randomized to placebo had an increase in body weight. In contrast, subjects randomized to stay on semaglutide continued to lose weight. The proportion of subjects who had at least 5% bw loss was greater in semaglutide compared to placebo in STEP 1, STEP 2, and STEP 3.

Table 11: Percent Change in Body Weight from Baseline to Week 68: Primary Endpoints

Primary endpoint: %change in bw				
		N (obs)	LS mean[1] (SE)	Treatment Difference [95% CI]; p-value
STEP 1	Sema 2.4 mg	1306 (1212)	-14.85 (0.29)	-12.44 [-13.26, -11.61]; <0.0001
	Placebo	655 (577)	-2.42 (0.31)	
STEP 2	Sema 2.4 mg	404 (388)	-9.64 (0.36)	-6.21 [-7.28, -5.15]; <0.0001
	Placebo	403 (376)	-3.42 (0.41)	
STEP 3	Sema 2.4 mg	407 (373)	-15.97 (0.55)	-10.26 [-11.83, -8.69]; <0.0001
	Placebo	204 (189)	-5.71 (0.59)	
STEP 4*	Sema 2.4 mg	535 (520)	-7.88 (0.36)	-14.75 [-15.99, -13.51]; <0.0001
	Placebo	268 (250)	6.87 (0.52)	
Primary endpoint: ≥5% bw loss				
		N (obs)	Proportion[2] (%)	Treatment Difference [95% CI]; p-value
STEP 1	Sema 2.4 mg	1306 (1212)	83.47	52.41 [48.06, 56.75]; <0.0001
	Placebo	655 (577)	31.07	
STEP 2	Sema 2.4 mg	404 (388)	67.44	37.25 [30.68, 43.81]; <0.0001
	Placebo	403 (376)	30.20	
STEP 3	Sema 2.4 mg	407 (373)	84.79	37.04 [28.90, 45.19]; <0.0001
	Placebo	204 (189)	47.75	

Abbreviations: N=number of subjects randomized; bw=body weight; obs=number of observed; sema=semaglutide; LS mean= least squares mean; SE: standard error; CI=confidence interval; [1]Model based estimates and standard error, the ANCOVA model included treatment, stratification factors (STEP 2 only) as fixed effects and baseline value as a covariate; [2]Estimates using a logistic regression with treatment (and stratification factors in STEP 2) as a factor and baseline body weight (kg) as a covariate; Missing observations were multiple imputed (1000 times) from retrieved subjects of the same randomized treatment; *In STEP 4, baseline was at Week 20 (randomization); [Source: Reviewer]

Pre-specified sensitivity analyses using different imputation approaches (J2R-MI, single imputation, MMRM, and non-responder analysis) were conducted to evaluate the robustness of the conclusions based on the primary analysis. All sensitivity analyses yielded results that were consistent with the primary analysis results. Two-dimensional tipping point analyses with penalties (from -30% to 30%) applied to both treatment groups were performed. For both treatment groups, no penalty reversed the conclusion of the primary analysis in the penalty range explored, supporting the robustness of the conclusion based on the primary analysis.

Key secondary endpoint results

In STEP 1, all key secondary endpoints were statistically significant supporting the efficacy of semaglutide compared to placebo (Table 12). The proportion of subjects who had at least 10% bw loss (or at least 15% bw loss) from baseline to Week 68 was greater in semaglutide compared to placebo. Changes in waist circumference and systolic blood pressure were statistically significant and the results indicated greater reductions in the semaglutide group than in the placebo group. Changes in SF-36 and IWQoL Lite-CT scores were statistically significant and the results indicated greater improvements in the semaglutide group than in the placebo group (High scores indicate favorable outcomes). Consistent results were observed with sensitivity analyses.

Table 12: Key Secondary Endpoints in STEP 1

	N (obs)	Proportion[1] (%)	Treatment difference [95% CI]; p-value
≥10% bw loss			
Sema 2.4 mg	1306 (1212)	66.13	54.10 [50.35, 57.85]; <0.0001
Placebo	655 (577)	12.02	
≥15% bw loss			
Sema 2.4 mg	1306 (1212)	47.92	43.08 [39.83, 46.33]; <0.0001
Placebo	655 (577)	4.84	
	N (obs)	LS mean (SE)[2]	Treatment difference [95% CI]; p-value
Waist circumference (cm)			
Sema 2.4 mg	1306 (1210)	-13.54 (0.27)	-9.42 [-10.23, -8.61]; <0.0001
Placebo	655 (575)	-4.13 (0.31)	
Systolic blood pressure (mmHg)			
Sema 2.4 mg	1306 (1210)	-6.16 (0.36)	-5.10 [-6.31, -3.89]; <0.0001
Placebo	655 (574)	-1.06 (0.50)	
SF-36 physical functioning score			
Sema 2.4 mg	1306 (1203)	2.21 (0.18)	1.80 [1.16, 2.45]; <0.0001
Placebo	655 (569)	0.41 (0.28)	
IWQoL_Lite-CT physical function score			
Sema 2.4 mg	1306 (1201)	14.68 (0.54)	9.44 [7.46, 11.42]; <0.0001
Placebo	655 (569)	5.24 (0.86)	

Abbreviations: N=number of subjects randomized; obs=number of observed; LS mean= least squares mean; SE: standard error; CI=confidence interval; SF-36=Short Form 36 v2.0 acute; IWQoL Lite-CT=Impact of Weight on Quality of Life-Lite for Clinical Trials; [1]Estimates using a logistic regression with treatment as a factor and baseline value as a covariate; ; [2]Model based estimates and standard error, the ANCOVA model included treatment as a fixed effect and baseline value as a covariate; Missing observations were multiple imputed (1000 times) from retrieved subjects of the same randomized treatment; [Source: Reviewer]

In STEP 2, all key secondary endpoints were statistically significant supporting the efficacy of semaglutide compared to placebo (Table 13). The proportion of subjects who had at least 10% bw loss (or at least 15% bw loss) was greater in semaglutide compared to placebo. Changes in waist circumference, HbA_{1c} and systolic blood pressure were statistically significant and the results indicated greater reductions in the semaglutide group than in the placebo group. The percent change in bw was greater in semaglutide 2.4 mg compared to semaglutide 1.0 mg, indicating greater weight loss in the semaglutide 2.4 mg than in the semaglutide 1.0 mg. Changes in SF-36 and IWQoL Lite-CT scores were statistically significant and the results indicated greater improvements in the semaglutide group than in the placebo group. Consistent results were observed from sensitivity analyses.

Table 13: Key Secondary Endpoints in STEP 2

	N	Proportion[1] (%)	Treatment difference [95% CI]; p-value
≥10% bw loss			
Sema 2.4 mg	404 (388)	44.47	34.29 [28.39, 40.20]; <0.0001
Placebo	403 (376)	10.18	
≥15% bw loss			
Sema 2.4 mg	404 (388)	25.05	20.74 [15.67, 25.81]; <0.0001
Placebo	403 (376)	4.31	
	N	LS mean (SE)[2]	Treatment difference [95% CI]; p-value
Waist circumference (cm)			
Sema 2.4 mg	404 (387)	-9.40 (0.37)	-4.88 [-5.97, -3.79]; <0.0001
Placebo	403 (375)	-4.52 (0.41)	
%change in bw			
Sema 2.4 mg	404 (388)	-9.64 (0.36)	-2.65 [-3.66, -1.64]; <0.0001
Sema 1.0 mg	403 (380)	-6.99 (0.37)	
HbA_{1c} (%)			
Sema 2.4 mg	404 (381)	-1.60 (0.07)	-1.23 [-1.42, -1.05]; <0.0001
placebo	403 (374)	-0.37 (0.07)	
Systolic blood pressure (mmHg)			
Sema 2.4 mg	404 (387)	-3.92 (0.73)	-3.43 [-5.57, -1.30]; 0.0016
Placebo	403 (376)	-0.49 (0.81)	
SF-36 physical functioning score			
Sema 2.4 mg	404 (381)	2.52 (0.39)	1.52 [0.44, 2.61]; 0.0061
Placebo	403 (374)	0.99 (0.39)	
IWQoL_Lite-CT physical function score			
Sema 2.4 mg	404 (381)	10.12 (1.04)	4.83 [1.79, 7.86]; 0.0018
Placebo	403 (374)	5.29 (1.14)	

Abbreviations: N=number of patients randomized; LS mean= least squares mean; SE: standard error; CI=confidence interval; SF-36=Short Form 36 v2.0 acute; IWQoL Lite-CT=Impact of Weight on Quality of Life-Lite for Clinical Trials; [1]Estimates using a logistic regression with treatment and stratification factors as factors and baseline value as a covariate; ; [2]Model based estimates and standard error, the ANCOVA model included treatment and stratification factors as fixed effects and baseline value as a covariate; Missing observations were multiple imputed (1000 times) from retrieved subjects of the same randomized treatment; [Source: Reviewer]

In STEP 3, all key secondary endpoints except SF-36 were statistically significant supporting the efficacy of semaglutide compared to placebo (Table 14). The proportion of subjects who had at least 10% bw loss (or at least 15% bw loss) was greater in semaglutide compared to placebo. Changes in waist circumference and systolic blood pressure were statistically significant and the results indicated greater reductions in the semaglutide group than in the placebo group. Change in SF-36 score was not statistically significant (p-value=0.1407), however, the result indicated a numerical improvement in the semaglutide group compared to the placebo group. Consistent results were observed from sensitivity analyses.

Table 14: Key Secondary Endpoints in STEP 3

	N	Proportion[1] (%)	Treatment difference [95% CI]; p-value
≥10% bw loss			
Sema 2.4 mg	407 (373)	72.96	45.88 [38.01, 53.74]; <0.0001
Placebo	204 (189)	27.08	
≥15% bw loss			
Sema 2.4 mg	407 (373)	53.45	40.20 [33.10, 47.30]; <0.0001
Placebo	204 (189)	13.24	
	N	LS mean (SE)[2]	Treatment difference [95% CI]; p-value
Waist circumference (cm)			
Sema 2.4 mg	407 (371)	-14.61 (0.58)	-8.33 [-9.97, -6.70]; <0.0001
Placebo	204 (189)	-6.27 (0.61)	
Systolic blood pressure (mmHg)			
Sema 2.4 mg	407 (372)	-5.53 (0.77)	-3.92 [-6.35, -1.48]; 0.0016
Placebo	204 (188)	-1.62 (0.98)	
SF-36 physical functioning score			
Sema 2.4 mg	407 (368)	2.41 (0.30)	0.84 [-0.28, 1.95]; **0.1407**
Placebo	204 (182)	1.58 (0.48)	

Abbreviations: N=number of subjects randomized; LS mean= least squares mean; SE: standard error; CI=confidence interval; SF-36=Short Form 36 v2.0 acute; [1]Estimates using a logistic regression with treatment as a factor and baseline value as a covariate; [2]Model based estimates and standard error, the ANCOVA model included treatment as a fixed effect and baseline value as a covariate; Missing observations were multiple imputed (1000 times) from retrieved subjects of the same randomized treatment; [Source: Reviewer]

In STEP 4, all key secondary endpoints were statistically significant supporting the efficacy of semaglutide compared to placebo (Table 15). Changes in waist circumference and systolic blood pressure were statistically significant and the results indicated greater reductions in the semaglutide group than in the placebo group. Change in SF-36 score was statistically significant and the results indicated greater improvements in the semaglutide group than in the placebo group. Consistent results were observed from sensitivity analyses.

Table 15: Key Secondary Endpoints in STEP 4

	N	LS mean (SE)[1]	Treatment difference [95% CI]; p-value
Waist circumference (cm)			
Sema 2.4 mg	535 (518)	-6.43 (0.36)	-9.73 [-10.89, -8.58]; <0.0001
Placebo	268 (248)	3.31 (0.46)	
Systolic blood pressure (mmHg)			
Sema 2.4 mg	535 (518)	0.49 (0.57)	-3.93 [-5.78, -2.08]; <0.0001
Placebo	268 (248)	4.42 (0.76)	
SF-36 physical functioning score			
Sema 2.4 mg	535 (516)	0.98 (0.16)	2.39 [1.53, 3.25]; <0.0001
Placebo	268 (245)	-1.41 (0.41)	

Abbreviations: N=number of subjects randomized; LS mean= least squares mean; SE: standard error; CI=confidence interval; SF-36=Short Form 36 v2.0 acute; [1]Model based estimates and standard error, the ANCOVA model included treatment as a fixed effect and baseline value as a covariate; Missing observations were multiple imputed (1000 times) from retrieved subjects of the same randomized treatment; [Source: Reviewer]

3.3 Evaluation of Safety

All safety analyses were conducted on the safety analysis set, which was defined as all randomized subjects who were treated with at least one dose of treatment. The results are summarized in Table 16. Adverse events were primarily driven by gastrointestinal (GI) events. More serious adverse events (SAE) were observed in the semaglutide group compared to the placebo except for STEP 2 where the percent of SAE were similar between semaglutide 2.4 mg and placebo.

In STEP 1, one subject in each treatment group died during the trial, due to sudden cardiac death (semaglutide 2.4 mg) and malignancy (placebo). In STEP 2, one subject in each treatment group died during the trial, due to myocardial infarction (semaglutide 2.4 mg), cardiorespiratory arrest (semaglutide 1.0 mg) and hepatocellular carcinoma metastatic (placebo). In STEP 3, there was no death during the trial. In STEP 4, one subject in each treatment group died during the trial, due to an undetermined cause (semaglutide 2.4 mg) and metastatic lung cancer (placebo), and both occurred during the randomized withdrawal period.

Table 16: Overview of Adverse Events

		Semaglutide 2.4 mg	Placebo	Semaglutide 1.0 mg
		N	N	N
STEP 1	Number of Subjects	1306	655	
	AE	1171 (89.7%)	566 (86.4%)	
	GI AE	969 (74.2%)	314 (47.9%)	
	SAE	128 (9.8%)	42 (6.4%)	
	Fatal event	1 (0.1%)	1 (0.2%)	
STEP 2	Number of Subjects	403	402	402
	AE	353 (87.6%)	309 (76.9%)	329 (81.8%)
	GI AE	256 (63.5%)	138 (34.3%)	231 (57.5%)
	SAE	40 (9.9%)	37 (9.2%)	31 (7.7%)
	Fatal event	1 (0.2%)	1 (0.2%)	1 (0.2%)
STEP 3	Number of Subjects	407	204	
	AE	390 (95.8%)	196 (96.1%)	
	GI AE	337 (82.8%)	129 (63.3%)	
	SAE	37 (9.1%)	6 (2.9%)	
STEP 4	Number of Subjects	534	268	
	AE	434 (81.3%)	201 (75.0%)	
	GI AE	224 (41.9%)	70 (26.1%)	
	SAE	41 (7.7%)	15 (5.6%)	
	Fatal event	1 (0.2%)	1 (0.4%)	

Abbreviations: N=number of subjects experiencing at least one event; AE=adverse event; GI=gastrointestinal; SAE=serious adverse event; [Source: excerpted from Section 12. Safety evaluation of CSR of each STEP trial]

For more details regarding the safety findings, refer to the review from the Medical Reviewer, Dr. Julie Golden.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analysis using an ANCOVA model compared %change from baseline at Week 68 in body weight across treatment groups within subgroups. The LS mean differences and the corresponding 95% CIs are shown in Figure 5 to Figure 8.

There were some random highs and random lows in sample estimates of subgroup treatment effect due to small sample size and large variability for some subgroups. Therefore, we also calculated shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. We used the same flat prior to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

For i=1, 2,..., Y_i represents the observed sample estimate of treatment effect in a subgroup level i, assume Yi ~ $N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 40^2)$, $1/\tau^2 \sim$ Gamma(0.001, 0.001)

A standard deviation of 40 was chosen so that the standard deviation was approximately 4 times subject-level standard deviation. Results from both the sample and shrinkage estimates of the treatment effects for the subgroups are presented in Figure 5 to Figure 8.

4.1 Gender, Race, Age, and Geographic Region

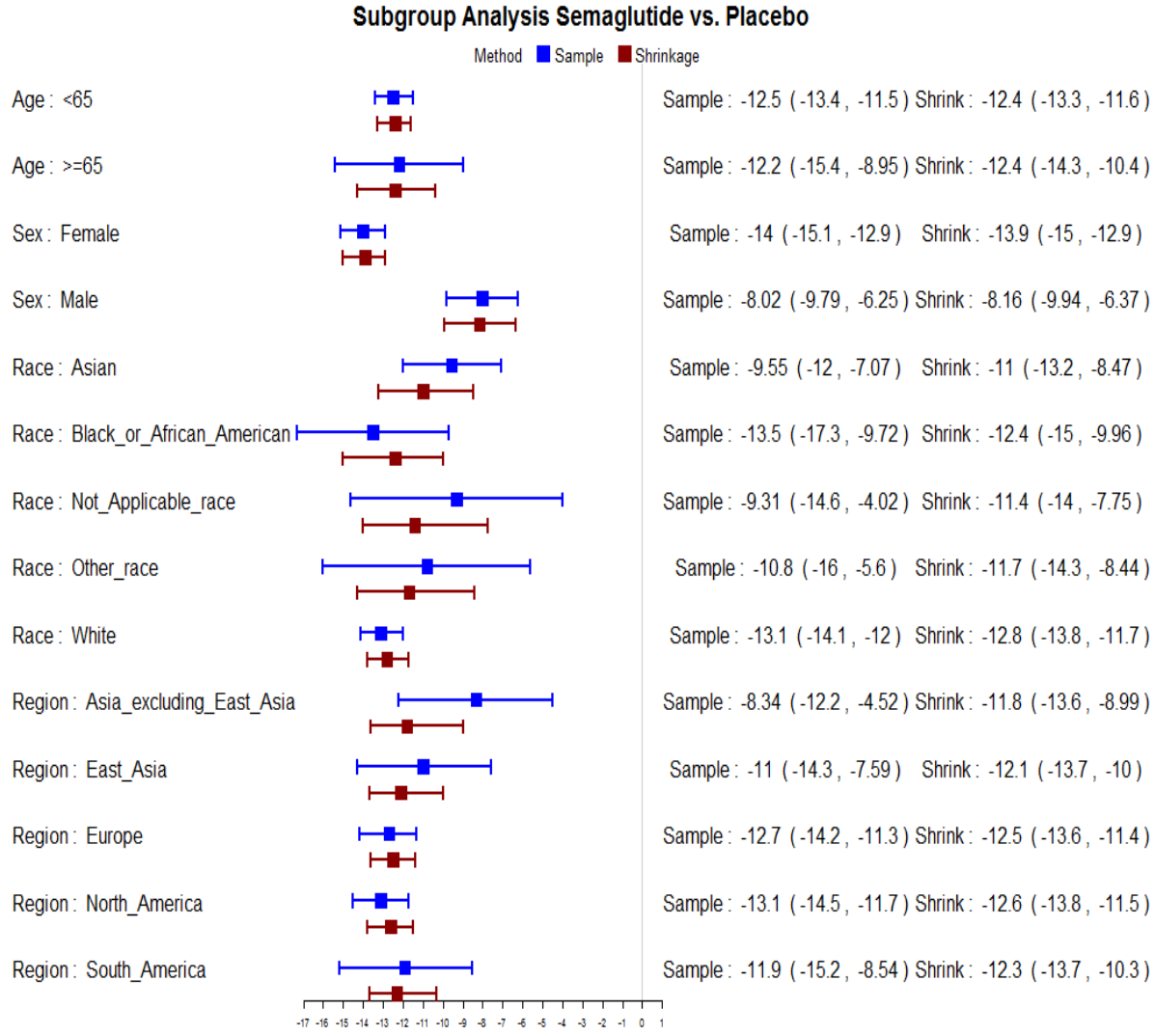
For subgroup analysis, "Other" category in race consisted of several race categories combined (Native Hawaiian or Other Pacific Islander or American Indian or Alaskan Native or Other; see Section 2.2.3 of this review) because the number of subjects was too small to obtain reliable estimates.

All subgroups reported the upper limit of the 95% CI less than zero, in favor of semaglutide, except for Other_race in STEP 2 and Asian_or_Other in STEP 3. However, with shrinkage estimates, the upper limits of the 95% CI were all less than zero in these groups, in favor of semaglutide. For all subgroups, the LS mean differences were less than zero, indicating greater

numerical reduction in the semaglutide group than in the placebo group. Sample and shrinkage estimates were generally consistent with each other and in line with the overall treatment effect.

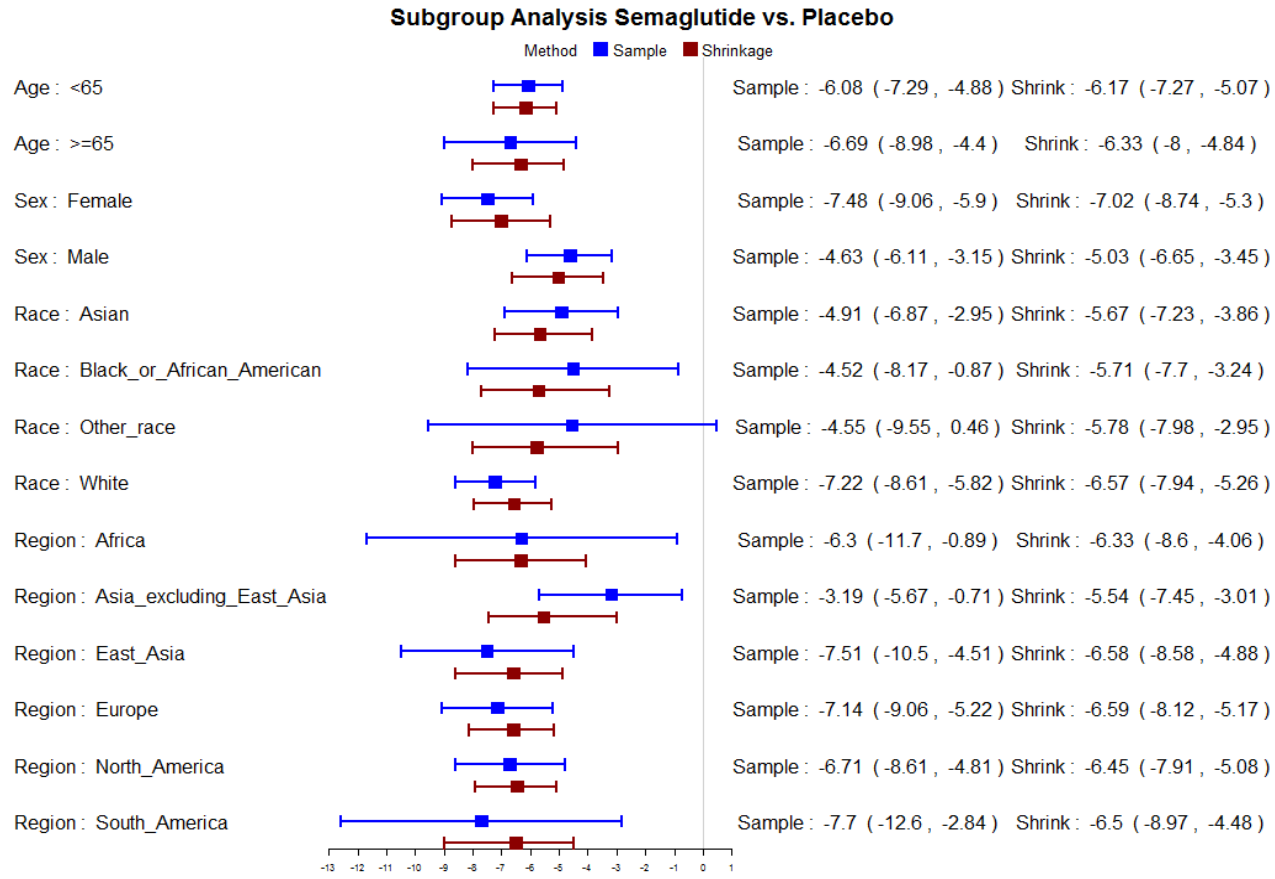
There were significant interaction effects between sex and treatment in STEP 1, STEP 2, and STEP 4. It appears that weight reduction was more favorable for females than for males in those trials. However, it will need further investigation to better understand the treatment effect on different sex.

Figure 5: STEP 1 Subgroup Results



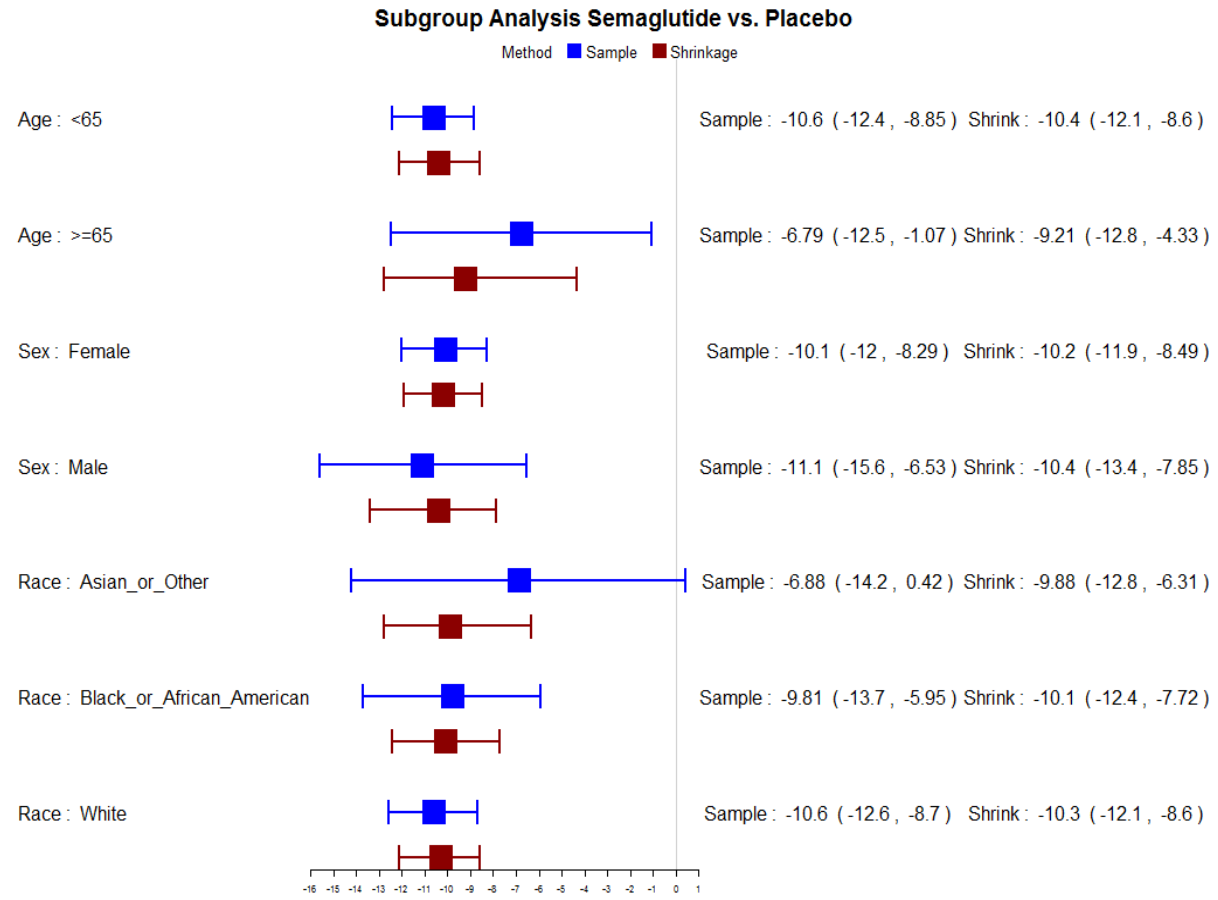
Sample estimates are shown with the corresponding 95% confidence interval (in blue) and shrinkage estimates are shown with the corresponding 95% credible interval (in red). Vertical line indicates zero; [Source: Reviewer]

Figure 6: STEP 2 Subgroup Results



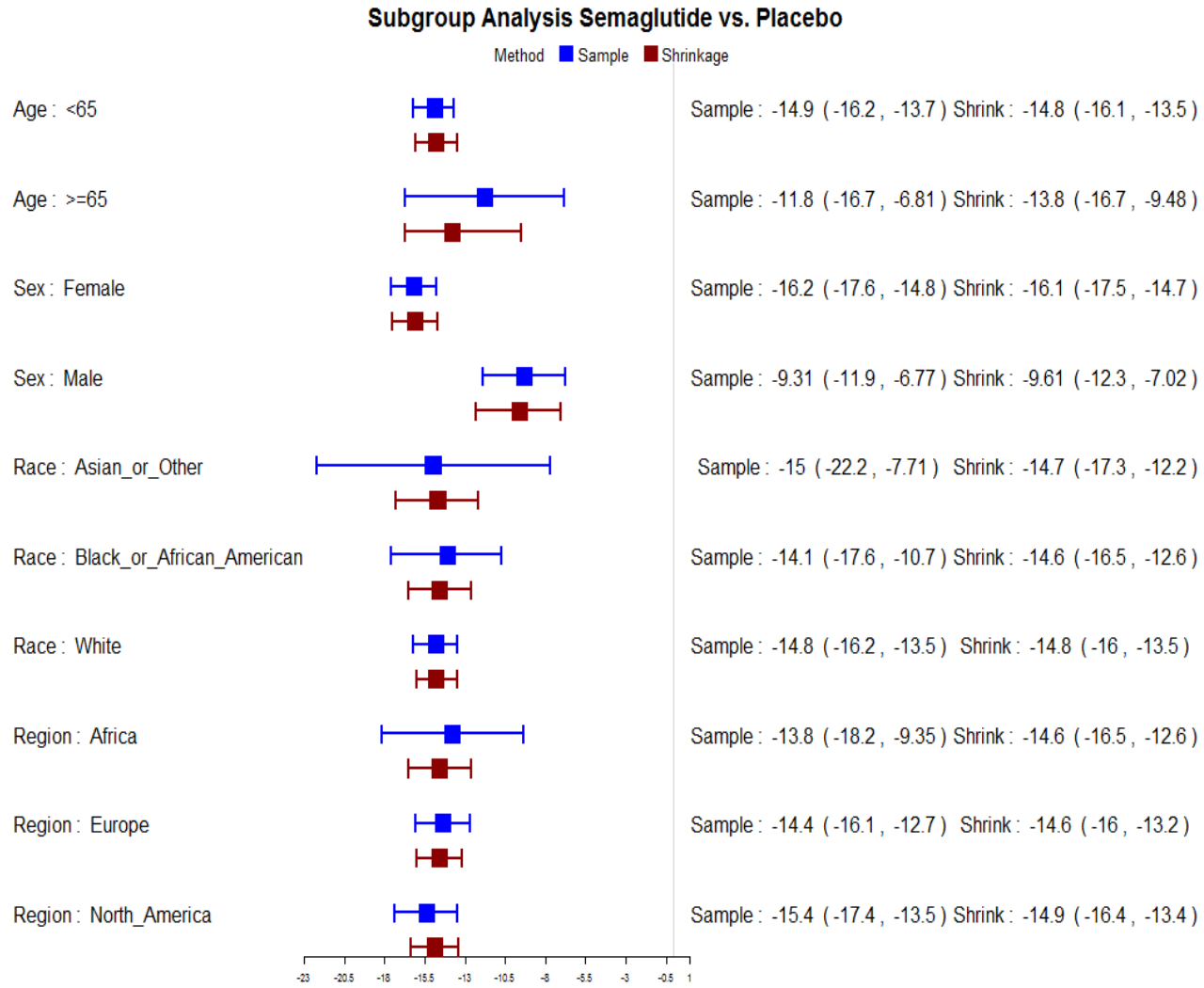
Sample estimates are shown with the corresponding 95% confidence interval (in blue) and shrinkage estimates are shown with the corresponding 95% credible interval (in red). Vertical line indicates zero; [Source: Reviewer]

Figure 7: STEP 3 Subgroup Results



Sample estimates are shown with the corresponding 95% confidence interval (in blue) and shrinkage estimates are shown with the corresponding 95% credible interval (in red). Vertical line indicates zero; [Source: Reviewer]

Figure 8: STEP 4 Subgroup Results



Sample estimates are shown with the corresponding 95% confidence interval (in blue) and shrinkage estimates are shown with the corresponding 95% credible interval (in red). Vertical line indicates zero; [Source: Reviewer]

4.2 Other Special/Subgroup Populations

STEP 4 was designed as a randomized withdrawal study with a 20-week run-in period followed by a 48-week randomized period (in a 2:1 ratio to either semaglutide 2.4 mg or placebo). It is of clinical interest to explore whether subjects with insufficient weight loss during the run-in period (Week 0 to Week 20) should stop treatment early. To assist the evaluation of weight loss, I conducted a series of exploratory analyses and the results are shown in

Table 17. Only subjects with observation at Week 68 (N=770; 520 subjects in semaglutide 2.4 mg and 250 subjects in placebo) were included for these exploratory analyses. The response rate was defined as the proportion of subjects who achieved 5% or more weight loss at Week 68 in comparison to run-in baseline.

Table 17 shows that subjects who achieved early stage weight reduction (20 weeks of the run-in) with semaglutide could still benefited from semaglutide with extended treatment (68 weeks). Subjects who achieved at least 5% weight loss in the run-in experienced high response rate of 93.7%. Subjects who achieved less than 5% weight loss during the run-in were further categorized by 1% to examine whether any early weight loss was closely related to the response rate. It appears subjects who had less than 2% loss had only 9.1% (1/11) response rate but the number of subjects was too small in this category. Table 17 also shows the treatment difference in percent change of weight at Week 68 by different ranges of weight loss at Week 20. The treatment difference at Week 68 becomes smaller when the weight loss at Week 20 less than 3%. However, only few (less than 4%) treated subjects had weight loss less than 3% at Week 20. Some of them still achieved 5% weight loss at Week 68.

For each subcategory of the %change in body weight during the run-in, treatment differences were obtained for the %change in body weight from Week 0 to Week 68 using a mixed model. The model included treatment as a fixed effect with unequal variance to account for unequal randomization.

Table 17: Subgroup Analyses by Run-in Weight Loss

%Change from Week 0 to Week 20	Semaglutide during randomized withdrawal period		Placebo during randomized withdrawal period		Treatment Mean Diff[2] [95% CI]
	N=520	Response rate[1]	N=250	Response rate	
<3% loss	20	8 (40.0%)	5	0 (0%)	-2.89 [-7.89, 2.10]
loss >=3%, <4%	20	8 (40.0%)	5	0 (0%)	-6.65 [-10.67, -2.64]
loss >=4%, <5%	22	16 (72.7%)	7	2 (28.6%)	-7.81 [-15.53, -0.08]
loss 5% or more	458	429 (93.7%)	233	117 (50.2%)	-13.52 [-14.76, -12.27]
No loss or gain	3	0 (0%)	0	0	
<1% loss	5	0 (0%)	1	0 (0%)	
<2% loss	11	1 (9.1%)	1	0 (0%)	
<3% loss	20	8 (40.0%)	5	0 (0%)	
<4% loss	40	16 (40.0%)	10	0 (0%)	
<5% loss	62	32 (51.6%)	17	2 (11.8%)	
5% or more loss	458	429 (93.7%)	233	117 (50.2%)	

Abbreviation: N=number of observations; CI=confidence interval; [1]Proportion of subjects who achieved 5% or more weight loss; [2]Obtained from an ANCOVA model assuming unequal variance for %change from Week 0 to Week 68; cell contents are frequencies with relative frequencies in parentheses; [Source: Reviewer]

It should be noted that these exploratory analyses were based on a subset of the STEP 4 dataset, using only subjects with observation at Week 68. The extent of missing data was small (4.1%), and the impact of missing data was not assessed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues that would impact or change the overall conclusions. The amount of missing data was not large throughout the studies and the sensitivity analyses using the pre-specified approaches supported the robustness of the primary efficacy results. Although not all key secondary endpoints were statistically significant, all of them were numerically in favor of semaglutide.

There were significant interaction effects between treatment and sex in three of the four trials, and it appears that weight reduction was more favorable for females than for males in those trials. However, the interactions were not qualitative. It will need further investigation to better understand the treatment effect on different sex.

5.2 Collective Evidence

The primary analysis showed statistically significant treatment effect in weight loss at Week 68. Secondary endpoints were consistently in favor of semaglutide. Sensitivity analyses also supported the robustness of the primary efficacy results.

5.3 Conclusions and Recommendations

The collective evidence from the submitted data demonstrated efficacy of semaglutide in the study population. I recommend approval for the proposed indication based on findings from the submitted results.

5.4 Labeling Recommendations (as applicable)

Reviewing of labeling is still ongoing while this statistical review is finalized.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KYUNGHEE K SONG
05/10/2021 03:15:53 PM

FENG LI
05/10/2021 03:24:50 PM

MARK D ROTHMANN
05/11/2021 08:51:51 AM
I concur